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Authors

Brazel, Danielle

Nagasaka, Misako

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COMMENTARY

MARIPOSA: Can Amivantamab and Lazertinib Replace Osimertinib in the Front-Line Setting?

Danielle Brazel[1], Misako Nagasaka[2,3]

[1]Department of Hematology/Oncology, Scripps Clinic/Scripps Green Hospital, La Jolla, CA, USA; [2]Department of Hematology/Oncology, University of California Irvine School of Medicine, Chao Family Cancer Center, Orange, CA, USA; [3]Department of Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

Correspondence: Misako Nagasaka, University of California Irvine School of Medicine Chao Family Cancer Center, 101 The City Drive, Orange, CA, 92868, USA, Email nagasakm@hs.uci.edu

Abstract: Osimertinib is the current first-line treatment for EGFR-mutated NSCLC, however, patients frequently relapse due to acquired resistance mutations. Amivantamab is a bispecific antibody against EGFR and MET alterations. Lazertinib is a tyrosine kinase inhibitor active against EGFR mutations including common resistance mutations. The MARIPOSA trial was designed to study if the combination of amivantamab plus lazertinib in untreated epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) patients would provide improved progression-free survival. Here, we discuss the rationale for the study and the early results of MARIPOSA.

Keywords: epidermal growth factor receptor (EGFR) mutations, first line treatment, bispecific antibody

Introduction

Lung cancer is one of the most common cancers worldwide, 80 to 85% of cases are non-small cell lung cancer (NSCLC).[1,2] Epidermal growth factor receptor (EGFR) alterations are one of the most common driver mutations, found in 10–15% of Western patients and 40–50% of Asian patients with lung adenocarcinoma.[3–8] The most common EGFR mutations, also known as classic EGFR mutations, are EGFR exon 19 deletions and EGFR L858R point mutations on exon 21.

Patients with classic EGFR mutations have a 5-year overall survival (OS) of 19%.[9] With the development of first-generation tyrosine kinase inhibitors (TKIs), the 5-year OS of EGFR-mutated NSCLC was 14.6% (95% CI 9.7–21.9).[10] With further development of second- and third-generation TKIs the 5-year OS rate has improved to 28% (95% CI 22.1–35.7).[11]

Osimertinib, a third-generation EGFR TKI is the current standard of care in the United States for first-line treatment of EGFR-mutated NSCLC. Although patients with EGFR mutations respond well to EGFR-targeted therapeutics, patients eventually relapse due to the development of resistance.

In May 2021, the Federal Drug Administration (FDA) approved amivantamab (Rybrevant, Janssen Biotech) for EGFR exon20 insertion mutations after progression on or after platinum-based chemotherapy.[12] Amivantamab is a bispecific antibody active against a wide range of EGFR and MET aberrations.[13,14]

Lazertinib (Leclaza, Janssen Biotech) is an oral third-generation TKI that inhibits EGFR mutations including classic EGFR mutations (exon 19 deletion and L858R exon 21 point mutation) and EGFR T790M resistant mutations while sparing wild-type EGFR cells.[15] Lazertinib is approved for use in Korea.

The MARIPOSA study investigated if the combination of amivantamab plus lazertinib would provide meaningful clinical benefit over single-agent osimertinib or lazertinib in the treatment naïve setting. Preclinical studies using the combination of amivantamab and lazertinib suggested synergistic inhibition of tumor growth. MARIPOSA met its primary endpoint of a statistically significant improvement in PFS using amivantamab plus lazertinib in treatment naïve EGFR-mutated NSCLC. Here, we review the data behind using the combination and the trial in greater detail.

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Pharmacokinetics

Amivantamab

In early phase I studies, amivantamab exposure increased proportionally at doses ranging from 250 mg to 1750 mg. Amivantamab concentration reached a steady state by cycle 4 with a half-life of 11.3 (± 4.5) days.[16] The recommended dose is 1050 mg for baseline body weight <80 kg and 1400 mg for body weight 80 kg or more. Amivantamab is administered intravenously weekly for 4 weeks then every 2 weeks until disease progression or toxicity.

Lazertinib

Lazertinib exposure increased proportionally at doses ranging from 20 to 320 mg with steady state reached by day 15.[17] There were no clinically relevant differences in exposure when lazertinib was taken with or without food.[18] The recommended dose is 240 mg daily.

Pharmacodynamics

Amivantamab

Amivantamab completely and durably saturates both EGFR and MET at doses of at least 700 mg.[16]

Lazertinib

In vitro studies found lazertinib was at least as potent as osimertinib, however, demonstrated less activity against wild-type EGFR.[19] In vitro studies of lazertinib showed higher selectivity and potency than osimertinib in both kinase assay and mutant EGFR Ba/F3 cells.[19] Lazertinib had less activity against wild-type EGFR compared to osimertinib. In T790M mutated EGFR activating cells, lazertinib resulted in greater tumor regression than osimertinib. Lazertinib also demonstrated high intracranial tumor/plasma and intracranial tumor/brain area under the concentration–time curve ratios of 7.0 and 7.9, respectively.

Amivantamab for EGFR Exon 20 Insertion

The phase I CHRYSALIS study examined the use of amivantamab in different settings and combinations. The initial FDA approval of amivantamab was based off of promising results in the exon20 insertions cohort of the CHRYSALIS study. In this platinum-pretreated population, ORR was 40% (95% CI 29–51) including 4% complete response.[16] The reported median duration of response (DOR) was 11.1 months (95% CI 6.9 – not evaluable) and median PFS 8.3 months (95% Ci 6.5–10.9).[20] The median OS 22.8 months (95% CI 14.6, not evaluable). The most common adverse effects were rash (86%), infusion-related reactions (65%), and paronychia (42%). Additional arms of the CHRYSALIS trial examined amivantamab monotherapy and in combination with chemotherapy.

Lazertinib as a 3rd Generation EGFR Inhibitor

Lazertinib was studied in the phase I/II LASER201 trial (NCT03046992, NCT04075396) which demonstrated an ORR 54% and lazertinib was well tolerated across all doses.[17,21] Lazertinib also demonstrated a similar ORR against central nervous system lesions.[17] In the phase III LASER301 study, lazertinib was compared to gefitinib in the front-line setting of EGFR-mutated NSCLC. The ORR was 76% in both groups (95% CI 0.62–1.59) with median DOR 19.4 months (95% CI 16.6–24.9) with lazertinib and 8.3 months (95% CI 6.9–10.9) with gefitinib.[22] Median PFS was 20.6 months versus 9.7 months with lazertinib and gefitinib respectively (HR 0.45, 95% CI 0.34–0.58). At interim data analysis, 18-month OS was similar between the groups (80% vs 72%, HR 0.74, 95% CI 0.51–1.08). The most common side effects reported were paresthesia (39%), rash (36%), and pruritis (27%). Lazertinib is approved for use in Korea.

Data on Amivantamab and Lazertinib Combination

Phase I/II Data

In one arm of the phase I CHRYSALIS trial, 20 patients with treatment-naïve classic EGFR-mutated NSCLC were treated with amivantamab plus lazertinib. The study population consisted of 11 EGFR exon 19 deletion and 9 L858R mutation cases. All patients responded initially to treatment with a 100% objective response rate (ORR).[23] At a median follow-up of 33.6 months, 10/20 (50%) were still on treatment including 7/11 (64%) with EGFR exon 19 deletion and 3/9 (33% L858R mutation).[24] The median DOR, median progression-free survival (PFS), and median OS were not

estimatable The estimated 24-month PFS was 65%. Dose interruptions, reductions, and discontinuations of either drug occurred in 35%, 40%, and 5% of patients, respectively.

Amivantamab-lazertinib was also studied in the post-osimertinib setting in the CHRYSALIS-2 study. In the post-osimertinib setting, amivantamab-lazertinib demonstrated an ORR of 36% (95% CI 22–51), median DOR 9.6 months (95% CI 5.3 – not reached), and median PFS 4.9 months (95% CI 3.7–9.5).[13] The safety profile was consistent to monotherapy with each agent and grade 3 or higher toxicities were reported in 4% of participants. Within this cohort, 77 patients had evaluable MET by immunohistochemical (IHC) staining.[25] Thirty-six percent were MET positive. The ORR for MET positive cases was 61% (95% CI 41–78) and 12% ((95% CI 5–25) in MET negative cases. Eighty-seven patients had detectable circulating tumor DNA (ctDNA) at baseline; however, ctDNA did not identify predictive biomarkers of treatment response.

MARIPOSA Study Design

The MARIPOSA trial enrolled 1074 patients. Inclusion criteria in the study included locally advanced or metastatic NSCLC, treatment-naïve for advanced/metastatic disease, identification of an EGFR exon 19 deletion or L858R point mutation. Patients were randomized in a 2:2:1 fashion across the following cohorts: Arm A (n=429) open-label combination therapy with amivantamab 1050 mg IV (or 1400 mg if >80 kg) weekly for four weeks then every 2 weeks plus lazertinib 240 mg daily; Arm B (n=429) double-blind osimertinib 80 mg daily; Arm C (n=216) double-blind lazertinib 240 mg daily. Patients were further stratified by EGFR mutation (exon 19 deletion or L858R point mutation), Asian race, and brain metastases. The primary endpoint was PFS using RECISTv1.1 criteria as assessed by blinded independent central review in comparison to Arm B osimertinib monotherapy. The secondary endpoints included OS, ORR, DOR, time to symptomatic progression, intracranial PFS, and safety.

Phase III Data

MARIPOSA (NCT04487080) was a phase III open-label study of treatment naïve EGFR-mutated NSCLC. The study was designed to assess the antitumor activity and safety of amivantamab plus lazertinib compared to osimertinib alone. Participants had a median age of 63-years-old and 59% were of Asian descent. Thirty-one percent reported a history of smoking and 40% had baseline brain metastases. EGFR mutation type included 60% exon 19 deletion and 40% L858R.

Amivantamab plus lazertinib reduced the risk of progression or death by 30% (95% CI 0.58–0.85, $p<0.001$).[26] The combination improved median PFS by 7.1 months (23.7 months on combination therapy; 95% CI 19.1–27.7 vs osimertinib 16.6 months; 95% CI 14.8–18.5) with HR 0.70 (95% CI 0.58–0.85). The lazertinib monotherapy arm also demonstrated clinically meaningful PFS of 18.5 months (95% CI 14.8–20.1). PFS benefit of amivantamab plus lazertinib was favored across all subgroups including age, gender, race, smoking history, brain metastases, and classic EGFR mutations. The PFS benefit in patients with brain metastases with amivantamab plus lazertinib was 18.3 months (95% CI 16.6–23.7) versus osimertinib 13.0 months (95% CI 12.2–16.4). Combination amivantamab plus lazertinib improved median DOR by 9 months (25.8 vs 16.8).

Although OS data was not finalized, at a median follow-up of 22.0 months, there was a non-statistically significant trend favoring amivantamab + lazertinib with HR 0.80 (95% CI 0.61–1.05).

Tolerability

The most common treatment-related adverse events occurring in at least 20% of participants included paronychia, infusion-related reactions, rash, hypoalbuminemia, increased ALT, and venous thromboembolism (37%).[26] EGFR- and MET-related adverse events were higher in the combination treatment group with the exception of diarrhea which was higher on osimertinib. The rate of interstitial lung disease or pneumonitis was around 3% in both treatment groups.

Treatment-related adverse events resulting in discontinuation of treatment were reported in 10% of patients on amivantamab plus lazertinib and 3% of patients on lazertinib. Grade 3 or higher treatment-related adverse events occurred in 316/421 (75%) on amivantamab plus lazertinib verses 183/428 (43%) on osimertinib.

Discussion

MARIPOSA met its primary endpoint of significantly prolonged PFS with amivantamab plus lazertinib versus osimertinib in the front-line setting. Although the combination regimen resulted in higher toxicity for participants, adverse events were largely grade 1 and grade 2. MARIPOSA has now introduced amivantamab and lazertinib as a novel front-line agent for patients with NSCLC harboring sensitizing EGFR mutations. This regimen may be beneficial for younger, more fit patients who are able to tolerate additional low-grade toxicities. This combination was also effective for EGFR-mutated patients with CNS metastases with PFS 18.3 months compared to 13.0 months on osimertinib. Additionally, the first-line combination treatment with amivantamab plus lazertinib has the advantage of intensified treatment without the addition of cytotoxic chemotherapy and may be favorable to patients whom platinum-based chemotherapy would be contraindicated or in those whom it would be preferable to have that option at a later time (ie initial low burden of disease).

Although patients with EGFR mutations respond well to EGFR-targeted therapeutics, patients inevitably relapse due to the development of resistance. The most common mechanisms of resistance to first-generation EGFR TKIs include EGFR T790M mutation, MET amplification, HER2 amplification or mutation, and small cell transformation.[27,28] Mechanisms of resistance to third-generation EGFR TKIs include development of C797S mutations, EGFR amplifications, and off target or EGFR independent mechanisms.[29] Overall, secondary EGFR and MET alterations account for 25–50% of tumor resistance.[30–32]

The phase III MARIPOSA-2 study (NCT04538664) also met its primary endpoint of a significant PFS improvement when using amivantamab, lazertinib, and chemotherapy compared to chemotherapy alone in patients with EGFR-mutated NSCLC after progression on osimertinib. Preliminary results presented at ESMO 2023 showed a median PFS of 8.3 months with the combination arm vs 4.2 months in the chemotherapy only arm.[33] PFS findings were similar across all subgroups including age, gender, race, weight, smoking history, and brain metastases. Although ORR was similar between the amivantamab-chemotherapy group and the amivantamab-chemotherapy-lazertinib group (64% vs 63%), the DOR was 6.9 months versus 9.4 months, respectively. Intracranial PFS was also similar between the arms (HR 0.55 and 0.58, respectively). However, PFS with the experimental arm was more pronounced in patients who had not received prior brain radiation with HR 0.36 versus HR 0.44. Amivantamab-containing regimens had higher rates of grade 3 or higher adverse events and dose modifications, highest in the amivantamab-chemotherapy-lazertinib arm at 92% vs 72% amivantamab-chemotherapy versus 48% chemotherapy alone. Rates of febrile neutropenia (2%, 2%, 8%) and grade 3–4 bleeding (0%, 1%, 3%) were low in the chemotherapy, amivantamab-chemotherapy, and amivantamab-chemotherapy-lazertinib arms, respectively. Venous thromboembolism was highest in the amivantamab-chemotherapy-lazertinib (22%) versus the amivantamab-chemotherapy arm (10%). Of note, the original study design was amended to start lazertinib after completion of carboplatin in an attempt to reduce hematologic toxicities.

The first-line treatment landscape for EGFR mutated NSCLC is rapidly evolving. FLAURA2 initial results were recently presented at the 2023 World Conference on Lung Cancer. A total of 557 patients with classic EGFR mutated NSCLC were randomized to osimertinib plus pemetrexed plus platinum chemotherapy (carboplatin or cisplatin) followed by maintenance osimertinib plus pemetrexed versus osimertinib monotherapy. Patients had not received prior systemic therapy for advanced NSCLC and stable CNS metastases were allowed on trial. The primary endpoint was PFS with secondary endpoints including OS, ORR, DOR, disease control rate (DCR), health-related quality of life, and safety. The primary endpoint of investigator assessed median PFS was 25.5 months (95% CI 24.7, not reached) in the combination arm compared to 16.7 (95% CI 14.1–21.3) in the monotherapy arm.[34] PFS using the combination regimen was similar in patients with and without brain metastases at 24.9 months (95% CI 22.0, not reached) and 27.6 months (95% CI 24.7, not reached), respectively. The chemotherapy-osimertinib group also demonstrated similar PFS based on mutation type at 27.9 months (95% CI 25.1, not reached) in exon 19 deletions and 24.7 months (19.5, 27.4) in L858R mutations. OS data were immature at the time of data analysis. The chemotherapy-osimertinib patients had higher rates of severe (grade 3 or more) adverse events (64% vs 27%). Treatment was also more likely to be discontinued due to an adverse event (48% versus 6%). The most common toxicities in the combination regimen include anemia (47%), diarrhea (44%), nausea (43%), and neutropenia (41%). Toxicities were generally lower with osimertinib monotherapy with the exception of diarrhea (41%). Rates of interstitial lung disease were similar in both arms at 3% and 4%, respectively.

The blinded independent review committee assessed median PFS of FLAURA2 showed an even better number compared to MARIPOSA, which was approaching almost 30 months, although it exposes patients to cytotoxic chemotherapy upfront and for a much longer period of time. While MARIPOSA avoids chemotherapy and its related toxicities, it is still intravenous therapy at this time which may be inconvenient for some and we must also not ignore the increased toxicities with combination therapy. Technically speaking, the ones who are destined to develop MET-related resistance from osimertinib alone could benefit the most from upfront use of the MARIPOSA regimen. Future endeavors should include identification of such cohorts of patients so that treatment could be personalized upfront to intensify when needed and de-intensify when such risks are low. Further considerations into social aspects such as need for transportation as well as frequent clinic visits in correlation to patient quality of life are also important avenues to explore.

Conclusions

The MARIPOSA study using amivantamab in combination with lazertinib met its primary endpoint of a significantly improved PFS. When compared to osimertinib, the standard of care front-line agent, patients on amivantamab plus lazertinib had a 7.1 month longer PFS. Although toxicity was higher with the combination regimen, the majority of adverse events were grade 1–2. Based on the findings in the MARIPOSA study, amivantamab plus lazertinib has shown to be an effective and tolerable front-line option for EGFR-mutated NSCLC and may replace single-agent osimertinib in some patients.

Abbreviations

AUC, area under the concentration–time curve; CI, confidence interval; ctDNA, circulating tumor deoxyribonucleic acid; DCR, disease control rate; DOR, duration of response; EGFR, epidermal growth factor receptor; FDA, Federal Drug Administration; HR, hazard ratio; Kg, kilogram; MET, mesenchymal–epithelial transition factor; Mg, milligrams; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI: tyrosine kinase inhibitor.

Data Sharing Statement

Not applicable to this study.

Ethics Approval and Consent to Participate

This report did not meet criteria for IRB approval.

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Disclosure

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